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Applicant: Raymond P. Warrell, Jr. *et al.*

Title: *PROCESS FOR PRODUCING ARSENIC TRIOXIDE FORMULATIONS AND METHODS FOR TREATING CANCER USING ARSENIC TRIOXIDE OR MELARSOPROL*

Serial No.: 10/425,785 Filing Date: April 30, 2003

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DECLARATION UNDER 37 CFR §1.132

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

10 September 2003

Sir:

I, Ralph Ellison, state that:

1. I am a consultant to Cell Therapeutics, Inc. (CTI), the exclusive licensee of the application in caption ("the application"). CTI acquired its rights in the application through its purchase of PolaRx Biopharmaceuticals, Inc, a company that I co-founded and ran. While at PolaRx I was responsible for all aspects of clinical development of Trisenox® (intravenous arsenic trioxide). In my current capacity as consultant, I work closely with the Trisenox® (intravenous aresenic trioxide) clinical development team. I am familiar with the claims pending in the application.

2. I received my medical degree in 1986 from the University Of The Witwatersrand, in Johannesburg, South Africa. Before the application was filed, I was the head of the Company that developed Trisenox and worked closely with Dr. Ray Warrell, an inventor named in the application who at that time was a hired consultant to PolaRx. PolaRx sponsored the development in the United States of a protocol for treating acute promyelocytic leukemia (APL) via weight-based dosing of arsenic trioxide (ATO).

3. Dosage schemes for cancer treatment generally are quite different than those for the treatment of other diseases. Because cancer typically is caused by an abnormal proliferation of the

patient's own cells, for example, the targeting of disease tissue and cells will be non-specific and, hence, will have a detrimental effect on the patient's healthy tissue and cells. Consequently, toxicities that are unacceptable in the treatment of an allergic reaction, an infectious disease, and many other conditions are considered acceptable in the treatment of cancer, given the often deadly nature of latter condition. A decision to use a potentially toxic drug in cancer therapy is based, therefore, on a risk/benefit analysis.

4. The approach to determining a safe dose for most non-cancer disease types takes into account the size of the patient by weight, and this frequently gives rise to the use of a fixed or "flat" dose for a class of patients, such as all adult patients. This approach eases the calculation of the dosage amount during treatment. In the oncology field, on the other hand, the primary method for balancing the safety and the efficacy of a drug treatment entails metering dose by reference to the surface area of the patient.

5. For example, Smorenburg *et al.* states that, in "medicine, most drugs for adult patients are administered at a flat-fixed dose....In contrast, in oncology, the dosage of nearly all cytotoxic drugs is based on body-surface area (BSA) of the patient."[1] That is, instead of using a ratio of milligrams of drug per kilogram of patient, the standard approach in cancer treatment couches dosage in terms of milligrams of drug per square meter of patient surface area. This makes for a much more complex calculation of the actual amount to dose during treatment.

6. The prevalence of surface area dosing in cancer therapy is due in part to the potentially complex pharmacokinetics of weight based dosing between species, using conversion factors. By contrast, conventional wisdom in cancer therapy applies a conversion factor of one (1) in relation to surface area-dosing pharmacokinetics between species. See Voisin *et al.*[2] and Freireich *et al.*[3] This simplifies the assessment of a proposed safe dose in a field where the balance of efficacy to toxicity can be very problematic, and BSA dosing therefore has become the gold standard in oncology. As recently as 2001, Gurney notes that, "until there is a better method, BSA-dosing will prevail since there has

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[1] *J. Clin. Oncology*, 21:197-202 (2003).

[2] *Regulatory Toxicology and Pharmacology*, 12:107-116 (1990).

[3] *Cancer Chemotherapy Reports*, 50:219-244 (1966).

been over 40 years of experience with this method and 'old habits die hard.'"[4] Thus, even while debate continues on current, BSA-based dose calculations for chemotherapy, oncologists principally employ BSA dosing to balance toxicity and efficacy based on patient size.

7. Those working in the oncology field sometimes consider flat dosing as an alternative to BSA dosing. For example, Westervelt *et al.* explored the adjusting of a flat dose of arsenic trioxide for a single APL patient.[5] In their 1997 abstract, Westervelt *et al.* flat-dosed the patient 10 mg of arsenic trioxide daily. In view of a resultant and profound leukocytosis, as well as other parameters indicating lack of efficaciousness, Westervelt *et al.* increased the dose to 50 mg/day. Having observed significant toxicity during and after the treatment, they concluded that toxicities had to be considered when dosing arsenic trioxide.[6]

8. In the course of developing a clinical protocol for treatment of APL with ATO, the present inventors also initially adopted a flat-dosing approach and, with their first five patients, used a daily 10-mg dose.[7] Patient 5 in the initial group relapsed within 24 days of achieving total remission and before completion of the consolidation therapy. As the patient was a very large individual (163 kg), the inventors questioned whether he might have received too little drug at a flat dose of 10 mg daily. The relevant literature did not suggest this problem, since there was no teaching that the size of a patient should be considered in arriving at an appropriate dosage.

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[4] *Brit. J. Cancer*, 86:1297-1302 (2001).

[5] Abstract 3859, *Blood*, 90 (Suppl. 1): 249b (1997)

[6] Westervelt *et al.* also back-calculated the administered flat doses, identifying them in weight-based terms, too. Thus, the initial 10 mg/day dose was translated to 0.08 mg/kg, and 50 mg/day dose to 0.40 mg/kg. *Id.* The fact that flat dosing was used for this initial patient is confirmed in a later article by Zhang *et al*, which again references "10 mg daily" and "50 mg daily" for this same patient, while characterizing the protocol for 4 subsequently-treated patients as being one "with the dosage based on actual body weight." In both the abstract and in this later study, it is suggested that full Phase I/II studies would be needed to determine a proper dosing level for a broad population. See Zhang *et al.*, *Modern Pathology*, 13:954-61 (2000). Another later study, reported by Westervelt *et al.*, *Blood*, 98:266-71 (2001), did undertake a dose escalation study in order to determine an appropriate dosage. Only Phase I has been reported, and no dose escalation beyond the initial dose of 0.1 mg/kg per day was undertaken, possibly because of the "2 unexpected deaths" among the first nine patients. Thus, the Phase I trial failed to determine a proper dosing level, and leaves open the question of whether a dose that results in both efficacy and acceptable toxicity can be achieved for this drug.

[7] The flat dosing was in accordance with earlier reports illustrated by Westervelt *et al.* (1997), *supra*, Shen *et al.*, *Blood*, 89:3354-3360 (1997), and Zhang *et al.*, *Chinese J. of Hematology*, 17(2) (1996).

9. Since the drug had been well tolerated by the initial patients, and in order to avoid the possibility of under dosing, as was believed to have occurred with Patient 5, the dose was increased to a 15 mg flat dose for all subsequent patients. This dosage amount was given to Patients 6 and 7. Patient 8 was a 13 year-old girl and of smaller stature, however. For this patient, therefore, the inventors chose to revert to the original, 10 mg-daily dosage, as a precaution against the possibility of overdosing. Patient 9 was a 9 year-old boy and, because of his size, was given a flat dose of only 5 mg daily. Patient 10 was given the newer dosage of 15 mg daily.

10. Upon reviewing the results for the first ten patients, the inventors concluded that the standard flat dosing method, per Shen and Zhang, appeared not to be efficacious for large people and was too toxic for small people. They further concluded that their initial approach of adjusting the flat dose was arbitrary and did not allow for a balancing of toxicity and efficacy in a treatment protocol to be used across a broad population of patients. Prior to treating Patient 11, therefore, the inventors decided to implement a technique other than flat dosing. Rather than turning to standard BSA dosing, the technique widely used by oncologists for dosing of chemotherapeutic drugs, the inventors chose to attempt to develop a weight-based dosing scheme. Employing data generated from the first ten patients, the inventors calculated a putative weight-based dose of 0.15 mg/kg daily. This dose was used for the next two patients and was ultimately chosen to complete the study and to conduct the pivotal phase III trial in which 40 patients participated. The results of this trial are reported in Soignet *et al.*, *J. Clin. Oncology*, 19:3852-3860, and showed that arsenic trioxide treatment is both safe and effective. Eighty-five percent of patients achieved clinical complete remission, and there were no treatment-related deaths.[8] Westervelt *et al.* contrasts the results achieved in the trial reported in Soignet *et al.* with the unexplained deaths in their study, noting that "in another series of 40 APL patients treated with 0.15 mg/kg per day arsenic trioxide for variable periods, no life-threatening arrhythmias or treatment-related deaths were reported."[9] While proffering various theories to explain the differing results, Westervelt *et al.* reached no conclusion on this point.

11. The results obtained in the trial reported in Soignet *et al.* led to approval by the FDA of arsenic trioxide (Trisenox). Subsequent to FDA approval of Trisenox , data on an additional 2,228

[8] Soignet *et al.* (2001), page 3854 ("clinical efficacy") and page 3856 ("adverse events").

[9] Westervelt *et al.* (2001), page 270.

patients (treated at doses of about 0.15 mg/kg per day or greater) have been collected, via post marketing surveillance and in clinical trials. To date no deaths attributed to arsenic associated arrhythmia have been reported, providing further evidence that treatment with arsenic trioxide is safe.

12. Subsequent to the present invention, another group of oncologists chose to modify flat dosing to a dosing based upon the patient's size; this, in recognition of a need to protect patients from toxic doses of ATO during the APL treatment. See Au *et al.*, *Annals of Oncology*, 14:752-57 (2003). Au *et al.* adopted a BSA dosing scheme, however. Thus, they described the use of BSA dosing in the context of treating a group of patient with relapsed APL. Initial treatment was on a flat-dosage basis for APL patients who underwent bone-marrow transplantation and ATO therapy. For double-relapse patients, however, the dosage was metered to take into account the size of the patient on a surface area basis. The difference in initial dosing and double-relapse dosing can only be interpreted as an acknowledgement of the need to balance toxicity and efficacy for the patients who had been weakened by extensive therapy beforehand. When faced with the same problem that the present inventors confronted, in other words, Au *et al.* resorted to more conventional treatment scheme, with dosing based upon patient surface area.

****

I hereby declare that all the statements made herein of my known knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Sept 11 2003
Date

Ralph Ellison

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Continued overleaf

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Original article

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Arsenic trioxide in comparison with chemotherapy and bone marrow transplantation for the treatment of relapsed acute promyelocytic leukaemia

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Background: The best overall treatment strategy for patients with acute promyelocytic leukaemia (APL) in relapse with chemotherapy, bone marrow transplantation (BMT) or arsenic trioxide (As_2O_3) based therapy remains undefined.

Patients and methods: We reviewed the clinical course and treatment outcome of 143 APL cases seen in four major hospitals in Hong Kong over a 10-year period.

Results: Complete remission (CR) was attained in 113 cases (79%) with all-*trans* retinoic acid (ATRA) and chemotherapy. Relapse occurred at a median of 16 months in 54 cases, with a 3-year disease free survival of 56%. Post-relapse treatment was successful in 41 cases (76%), giving an actuarial 3-year overall survival (OS) of 81% from CR1. Three different protocols were used: chemotherapy alone (n = 19), allogeneic BMT (n = 14) and an As_2O_3-based regimen (n = 21). Chemotherapy was associated with the highest treatment-related mortality (TRM) at 53%, giving a CR2 rate of 47%. TRM was 36% for BMT. The CR2 rate for the As_2O_3-based regimen was 100%, with no TRM. However, 38% of As_2O_3 treated patients had subsequent relapses, which were further salvaged in 75% by combined As_2O_3 plus ATRA. The actuarial OS for the three protocols leveled off by 2 years at 82% for As_2O_3, 43% for BMT and 23% for chemotherapy (P = 0.0004).

Conclusions: Our results suggest that As_2O_3 may be superior to chemotherapy and BMT for the treatment of APL in relapse.

Key words: acute promyelocytic leukaemia, allogeneic bone marrow transplantation, arsenic trioxide, relapse

Introduction

Acute promyelocytic leukaemia (APL) is characterised by t(15; 17)(q22; q21), which results in *PML/RARA* gene fusion. It is highly sensitive to all-*trans* retinoic-acid (ATRA), which acts as a differentiation agent [1], and arsenic trioxide (As_2O_3), which induces both differentiation and apoptosis [2]. Although APL blasts are very sensitive to chemotherapy, particularly anthracyclines [3], induction chemotherapy is associated with early death due mainly to haemorrhagic complications [4]. With the use of ATRA combined with chemotherapy, haemorrhagic complications can largely be avoided. However, up to 20% of patients still relapse, despite the use of chemotherapy and ATRA as consolidation and maintenance treatment [5].

In relapsed APL, the best treatment strategy remains contentious. Some patients are still responsive to ATRA and chemotherapy. Allogeneic bone marrow transplantation (BMT) may give lasting remissions, but the patient selection and timing for BMT are unresolved issues. Clinical and laboratory evidence indicates that As_2O_3 is a highly effective treatment for relapsed APL. However, the role of As_2O_3, in comparison with further chemotherapy or allogeneic BMT, has not hitherto been formally evaluated.

In this report, we studied the treatment results of newly diagnosed and relapsed cases of APL over a 10-year period, with a specific focus on evaluating the relative merits of chemotherapy, allogeneic BMT and As_2O_3 in the treatment of relapses.

Materials and methods

Patients

All patients with APL treated between 1991 and 2001 were included in the analysis. They were treated in four tertiary referral centres (Queen Mary Hospital, Queen Elizabeth Hospital, Tuen Mun Hospital, Pamela Youde Nethersole Hospital) that served over 70% of leukaemia patients in Hong Kong during that time period. The diagnosis of APL was based on marrow

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Table 1. Treatment and outcome of 54 patients with relapsed acute promyelocytic leukaemia

Regimens	*n*	Early deaths	CR (%)	Second relapse, % (median time)	Outcome of further relapses
Chemotherapy	19	53% (bleeding, sepsis)	47	22 (2/9) at 11 months and 21 months	Both died
BMT	14	36% (mucositis, sepsis)	64	11 (1/9) at 40 months	CR with second BMT
As_2O_3	21	-	100	38 (8/21) at 13 months	Two died, six in CR with As_2O_3 + ATRA

CR, complete remission; BMT, bone marrow transplantation; As_2O_3, arsenic trioxide; ATRA, all-*trans* retinoic acid.

Table 2. Outcome of 14 acute promyelocytic leukaemia patients treated with allogeneic bone marrow transplantation (BMT)

	Sex/age (years)	Time	Status	Conditioning	Engraftment		GvHD	OS	DFS	Complications
					Plt >25	ANC >1				
1	M/22	4.0	R1	BuCy	24	18	0	122.9+	35.4	Relapse, 2nd BMT done
2	F/22	20.4	CR2	BuCyTBI	20	19	2	55.7	55.7	Died of bronchiolitis obliterans
3	F/30	10.3	CR2	BuCyTBI	23	19	3	98.9+	98.9+	cGvHD
4	F/14	17.9	CR2	BuCyTBI	13	17	2	93.5+	93.5+	Hemorhagic cystitis
5	M/39	20.1	R1	BuCyTBI	44	24	4	3.1	3.1	Die of sepsis
6	M/27	6.1	R1	BuCy	34	15	2	85.6+	85.6+	AVN of hip
7	F/12	5.8	R1	BuCy	27	30	2	13.3	13.3	Died of sepsis
8	M/35	17.7	R1	BuCyTBI	24	20	2	6.2	6.2	Died of mucositis
9	M/32	46.1	CR2	BuCyTBI	27	19	2	7.2	7.2	Died of sepsis
10	F/45	16.6	CR2	BuCyTBI	20	24	4	1.4	1.4	Died of liver failure
11	F/14	22.1	CR2	BuCy	18	15	0	64.2+	64.2+	Nil
12	M/45	22.1	CR2	BuCyTBI	14	15	2	9.7	9.7	Died of liver failure
13	F/47	15.7	CR2	BuCyTBI	28	25	2	3.7	3.7	Died of sepsis
14	F/35	19.0	CR2	BuCyTBI	13	18	2	45.5+	45.5+	cGvHD, transient graft failure[a]

M, male; F, female; time, time from initial diagnosis to BMT in months; R, relapse; CR, complete remission; Bu, busulphan; Cy, cyclophosphamide; TBI, total body irradiation; Plt >25, days to platelet count >25 × 10^9/l; ANC >1, days to absolute neutrophil count >1 × 10^9/l; GvHD, acute graft-versus-host disease (grades 0–4); OS, overall survival in months; DFS, disease-free survival in months; +, survivor; cGvHD, chronic graft-versus-host disease; AVN, avascular necrosis of hip.

[a]One month of marrow aplasia with spontaneous recovery due to idiosyncratic hypersensitivity to azathioprine for GvHD.

morphology, and was confirmed by cytogenetic and/or molecular investigations [6].

Treatment of newly diagnosed APL

The standard induction protocol was ATRA (45 mg/m²/day ×6 weeks), together with daunorubicin (50 mg/m²/day ×3 days) and cytosine arabinoside (100 mg/m²/day ×7 days). Consolidation therapy consisted of two to four courses of an anthracycline (daunorubicin or mitoxantrone) containing regimen. Maintenance therapy (ATRA 45 mg/m²/day ×15 every 3 months, methotrexate 15 mg/m²/week, 6-mercaptopurine 50 mg/m²/day for 18 months) was used in three centres. Prospective monitoring of minimal residual leukaemia was not performed routinely.

Treatment of relapsed APL

All relapses were diagnosed by marrow biopsy and confirmed cytogenetically or molecularly (Table 1). From 1991 to 1997, chemotherapy and ATRA were used for induction of second complete remission (CR2) (n = 33). Patients reaching CR2 and with a suitable marrow donor (n = 14) proceeded to allogeneic BMT, while the others (n = 19) received consolidation with conventional chemotherapy. After 1997, As_2O_3 (10 mg daily until remission) and idarurbicin (72 mg/m² in nine divided doses over 3 months) were used in all relapsed cases (n = 21), as previously reported [7]. Patients who relapsed again after As_2O_3/idarubicin treatment (n = 8) were further treated with As_2O_3 (10 mg/m²/day) and ATRA (45 mg/m²/day) until CR3, followed by further consolidation with As_2O_3 plus ATRA, each given for 14 days every 4–6 weeks for six courses, as reported previously [8].

Allogeneic BMT

From 1991 to 1997, all relapsed patients reaching CR2 and with a human leukocyte antigen (HLA)-identical donor (n = 14; 13 from siblings and one from a matched-unrelated donor) were considered suitable for allogeneic BMT (Table 2). There were no exclusion criteria. Conditioning regimen comprised: busulphan (16 mg/kg) and cyclophosphamide (120 mg/kg) in four cases; and busulphan (7 mg/kg), cyclophosphamide (50 mg/kg) and total body irradiation (TBI; 12 Gy) in 10 cases. Melphalan (100 mg/m²) and TBI (12 Gy) was used for the second BMT in one patient (case 1; Table 2). Cyclosporine and methotrexate was used in all cases for graft-versus-host disease (GvHD) prophylaxis.

Statistical analysis

Data were censored on the last day of 2001. For the whole group, actuarial survival was calculated by Kaplan–Meier analysis. Patients with or without

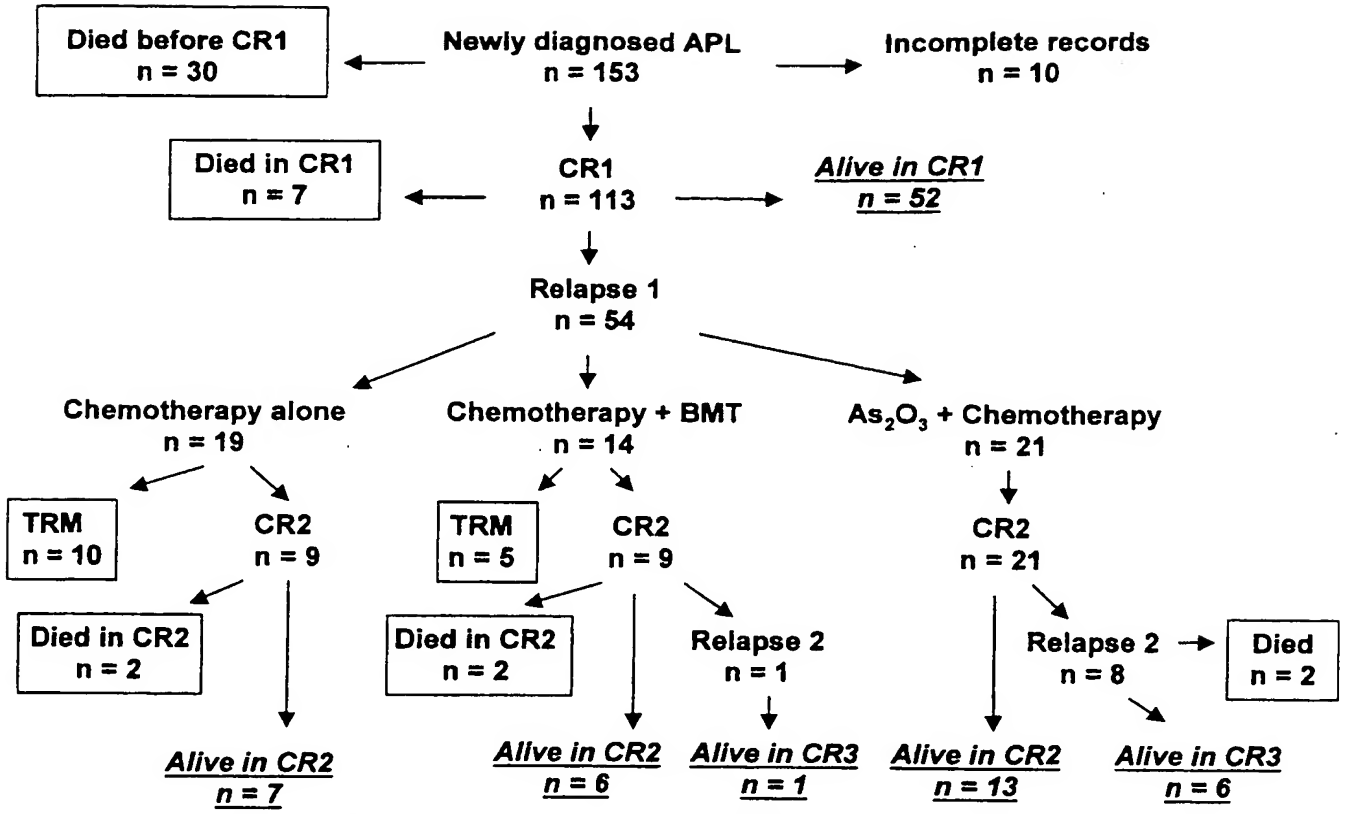

Figure 1. Treatment protocol and outcome of 153 cases of newly diagnosed acute promyelocytic leukaemia. CR, complete remission; BMT, allogeneic bone marrow transplantation; As_2O_3, arsenic trioxide; TRM, treatment-related mortality.

maintenance therapy were compared by log-rank test. Overall survival (OS) was calculated from the day of diagnosis to the day of death or censorship. Disease-free survival (DFS) was calculated from the day of diagnosis to the day of confirmed marrow relapse. For salvage cases, analysis of OS was from the day of relapse to the day of death or censorship. The log-rank model was used to analyse differences in OS for the three different treatment methods for relapses (chemotherapy, BMT, As_2O_3-based treatment).

Results

Treatment outcome of newly diagnosed APL

A total of 153 patients were diagnosed with APL within the study period (Figure 1). Complete data for analysis were available in 143 patients. A total of 30 patients died before or during induction chemotherapy. CR1 was achieved in 113 cases. Relapses occurred in 54 patients, at a median of 13 months (range 5–96 months). Late relapses, defined as relapses occurring 2 years after CR1, occurred in 10 cases. The 5-year actuarial DFS from CR1 was 42%. This did not differ significantly for patients with (n = 59) and without (n = 54) maintenance therapy (P = 0.087), owing to the occurrence of more late relapses in the latter group (Figure 2).

Treatment outcome of APL in first relapse

The results of different treatment groups (chemotherapy alone, n = 19; chemotherapy followed by allogeneic BMT, n = 14; As_2O_3 followed by chemotherapy, n = 21) are shown in Table 1 and Figure 3. Ten patients treated with chemotherapy and five patients receiving BMT died from early treatment-related complications. Two patients receiving BMT died from late complications (hepatitis B virus-related liver failure and bronchiolitis obliterans) (Table 2). Durable CR2 was achieved in 30 cases.

Treatment of APL in second or more advanced relapses

There were 11 further relapses at a median of 11 months (range 8–48 months) (Table 1). Both patients in the chemotherapy group received further chemotherapy, and died from treatment-related complications. The only patient who relapsed again in the BMT group received a second allogeneic BMT from an HLA-identical sibling, and has remained in CR3. Two patients in the As_2O_3 group died before further treatment could be given. Six patients achieved and have remained in remission, with combined As_2O_3 plus ATRA therapy.

Statistical analysis

The 2-year actuarial OS from R1 leveled off at 23% for the chemotherapy group, 43% for the BMT group and 82% for the As_2O_3 group (Figure 3). As a result of efficient salvage of advanced relapses, the 5-year actuarial OS from CR1, at 68%, was much better than the DFS.

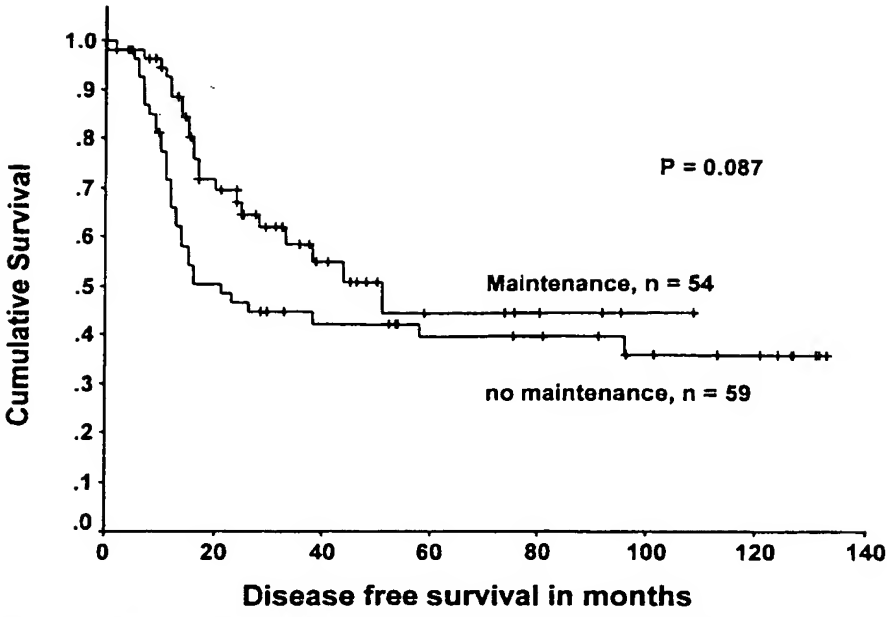

Figure 2. Disease-free survival in 113 acute promyelocytic leukaemia patients with or without maintenance chemotherapy after achieving first complete remission.

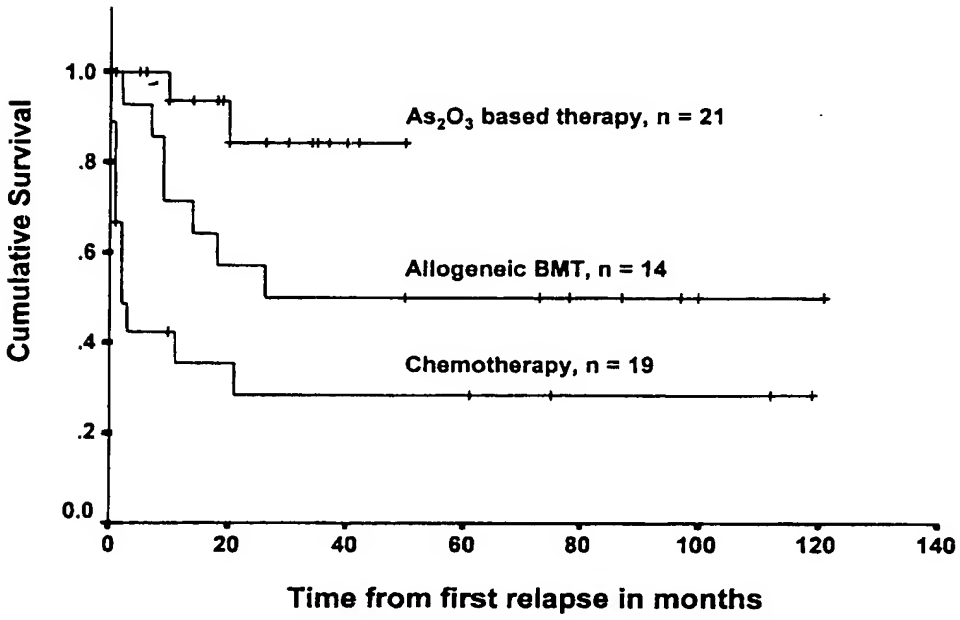

Figure 3. Overall survival of 54 patients with relapsed acute promyelocytic leukaemia treated with arsenic trioxide (As_2O_3)-based therapy, allogeneic bone marrow transplantation (BMT) and chemotherapy.

Discussion

With ATRA and chemotherapy as the induction regimen, the CR rate of 79% observed in this study is comparable to those of 72% and 96% reported previously [9]. However, our 5-year DFS, at 42%, was apparently inferior to the reported 3-year DFS of 86% to 90% in other series [10]. A number of reasons might account for this. One of the four centres in our study has not used maintenance therapy, which has been shown to be of beneficial effect in reducing relapses [11]. Furthermore, chemotherapy tolerance appears to be poor in Chinese people, and full-dose mercaptopurine maintenance was not achievable in most cases [12].

In relapsed APL, allogeneic BMT, chemotherapy and As_2O_3 are all useful treatment modalities, but the best choice and timing of treatment is as yet undefined [13]. Reported data on the use of ATRA plus chemotherapy for relapsed APL showed that only

29–35% of patients could be induced into durable remission [14, 15]. Allogeneic BMT for relapsed patients who achieved a second remission after ATRA plus chemotherapy also gave poor results. In one study, the leukaemia-free survival (LFS) was 22%, relapse rate (RR) was 54%, and the treatment-related mortality (TRM) was 40% [16]. In another study, only two of 11 APL patients in second remission survived the transplantation [17]. Data published by the European Blood and Marrow Transplantation (EBMT) Group showed that in 127 relapsed APL patients who received allogeneic BMT, the LFS was 53–61%, the RR was 10–22% and the TRM was 32–34% [18]. The data from the EBMT appeared to be slightly better than the former two studies, which could be related to different patient selection. However, these studies all showed that allogeneic BMT in APL patients in second remission was associated with a high TRM and an overall unsatisfactory outcome. As for As_2O_3, although a high remission rate can be achieved, the long-term follow-up results are less well defined. In two series comprising 87 relapsed cases, the 18- and 24-month LFS was 56% and 42%, respectively [19, 20].

In comparison with the studies of relapsed APL described above, our data offer a few advantages. This study involved a consecutive series, so that bias related to patient selection for various treatment options was diminished. This was particularly important for BMT, where patient selection could often affect the treatment outcome. Furthermore, the treatment and supportive care were similar. Our results might therefore give a better perspective on the relative merits of the different treatment options in relapsed APL.

We showed that with a follow-up of 3 years, treatment results for BMT were comparable to chemotherapy, but inferior to arsenic-based treatment for relapsed APL. The lower relapse rate with BMT was offset by the high early TRM, a phenomenon also observed in other studies [16–18]. Although few late relapses occurred after BMT, the survival curve remained unstable owing to late deaths from GvHD and organ toxicity. Furthermore, survivors after BMT might still suffer from the permanent side effects of immunosuppression, exposure to alkylating agents, infertility, premature menopause and increased risks of secondary malignancies. In contrast, As_2O_3-based therapy was associated with minimal toxicity or mortality. Although As_2O_3-induced second remissions were apparently associated with more subsequent relapses, long-term remission after combination therapy with As_2O_3 and ATRA might still be achieved in these patients [8]. Furthermore, the lack of organ damage meant that further relapses might still be salvaged by allogeneic BMT, although this was not required in any of our cases. Our results therefore suggest that As_2O_3-based therapy may be the treatment of choice for APL in first or more advanced relapses. For this reason, we have not performed BMT in any APL patients after 1997.

In conclusion, the availability of effective first-line and salvage therapy means that APL patients in any stage of their illness should be treated with curative intent, even when they have late advanced diseases [13]. As_2O_3 appears to be the best option for relapsed cases. The high efficacy of As_2O_3 in inducing second remissions means that optimal consolidation and maintenance of remission are key factors that will improve the cure rate. For allogeneic BMT to be offered as a consolidation, TRM must be improved. On the other hand, APL in advanced and repeated relapse appears to continue to respond to As_2O_3 treatment, which is associated with minimal side effects. Among these options, our data with short-term follow-up seemed to favour the use of repeated courses of As_2O_3. However, prospective clinical trials are needed to fully resolve the issue of As_2O_3 as compared with allogeneic BMT as the optimal treatment for relapsed APL.

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